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10/089,514	03/29/2002	Koji Yanai	2002_0451A	7814

7590 10/18/2005

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Suite 800  
2033 K Street NW  
Washington, DC 20006

EXAMINER
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KAM, CHIH MIN

ART UNIT	PAPER NUMBER
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1656

DATE MAILED: 10/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)	
	10/089,514	YANAI ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 26 July 2005.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1,5-7,17,19-21,23 and 25-37 is/are pending in the application.
- 4a) Of the above claim(s) 23 and 25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,5-7,17,19-21 and 26-37 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 March 2002 is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                                   | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>7/26/05</u>   | 6) <input type="checkbox"/> Other: _____                                    |

## DETAILED ACTION

### *Status of the Claims*

1. Claims 1, 5-7, 17, 19-21, 23 and 25-37 are pending.

Applicants' amendment filed July 26, 2005 is acknowledged. Applicants' response has been fully considered. Claims 1, 5-7, 17, 19-21, 23, 25, 26, 28 and 30 have been amended, claims 2-4, 8-16, 18, 22 and 24 have been cancelled, and new claims 32-37 have been added. Upon consideration, nucleotide sequences SEQ ID NO: 3 and 5, and nucleotides encoding amino acid sequences SEQ ID NO: 2, 4 and 6 will be included for examination. Claims 23 and 25 are non-elected inventions and withdrawn from consideration. Therefore, claims 1, 5-7, 17, 19-21, and 26-37 are examined.

### *Withdrawn-Objections to the Specification*

2. The previous objection to the specification is withdrawn in view of applicant's submission of a new abstract, applicant's amendment to the specification, and applicant's response at page 14 in the amendment filed July 26, 2005.

### *Withdrawn-Claim Objections*

3. The previous objection to claims 6 and 10-22 is withdrawn in view of applicant's cancellation of the claim, applicant's amendment to the claim, and applicant's response at page 14 in the amendment filed July 26, 2005.

### *Withdrawn Claim Rejections - 35 USC § 112*

4. The previous rejection of claims 8-16, 18 and 22, under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicants' cancellation of the claim in the amendment filed July 26, 2005.

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5. The previous rejection of claims 20 and 21, under 35 U.S.C. 112, first paragraph, regarding the deposited material, is withdrawn in view of applicants' deposit receipts submitted with the filing of the application, and applicant's response in the amendment filed July 26, 2005.

6. The previous rejection of claims 1-20 and 22, under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicants' cancellation of the claim, applicant's amendment to the claim, and applicant's response at pages 14-15 in the amendment filed July 26, 2005.

**Withdrawn Claim Rejections - 35 USC § 101**

7. The previous rejection of claims 26-27, under 35 U.S.C. 101, is withdrawn in view of applicants' amendment to the claim in the amendment filed July 26, 2005.

**Withdrawn Claim Rejections - 35 USC § 102**

8. The previous rejection of claims 1-5 and 18 under 35 U.S.C. 102(b) as anticipated by Blanc *et al.* (Mol. Microbiology 23, 191-202 (1997)), is withdrawn in view of applicants' amendment to the claim, applicants' cancellation of the claim and applicant's response at pages 18-19 in the amendment filed July 26, 2005.

**New Claim Rejections - 35 U.S.C. § 112**

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 5-7, 19-21, 33 and 35-37 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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10. Claim 5 is indefinite because of the use of the term of "at least one amino acid selected from .....and phenyllactic acid". The term cited renders the claim indefinite, it is not clear how phenyllactic acid can be an amino acid since it does not contain an amino group.

11. Claims 1, 5-7, 19-21, 33 and 35-37 are indefinite because of the use of the term "one to several modifications". The term cited renders the claim indefinite, it is not clear how many modifications are intended for the modified sequences, e.g., is it 5, 10, 20, 50 or 100?

Claims 5-7, 19-21 and 35-37 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

***Maintained Claim Rejections - 35 U.S.C. § 112***

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Previous rejection of claims 1, 5-7, 19-21 and 26 under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is maintained, and claims 28, 30, 32, 33 and 35-37 are added. The response to applicants' argument is indicated below.

The instant claims are drawn to transformants comprising a polynucleotide (or the polynucleotide itself), wherein the polynucleotide sequence encodes SEQ ID NO:2 or a modified sequence of SEQ ID NO:2 having 4-amino-4-deoxychorismic acid synthase activity, the polynucleotide sequence encodes SEQ ID NO:4 or SEQ ID NO:4 having 4-amino-4-

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deoxychorismic acid mutase activity, and/or, the polynucleotide sequence encodes SEQ ID NO:6 or SEQ ID NO:6 having 4-amino-4-deoxyphenic acid dehydrogenase activity.

The Court of Appeals for the Federal Circuit has recently held that a “written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as be structure, formula [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials.” *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at \*23, quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, genes encoding a synthase (papA), mutase (papB), and dehydrogenase (papC) of the claimed invention are described from *S. venezuelae* (SEQ ID NOs: 1-6); the prior art teaches analogous genes from *S. pristinaespiralis* (see Blanc *et al.*). The instant claims are drawn to, for example (claim 1), a polynucleotide encoding “the amino acid sequence of SEQ ID NO:2 or a modified sequence of SEQ ID NO:2 having 4-amino-4-deoxychorismic acid synthase activity” wherein said modification is defined as one or more (e.g., one to several) substitutions, deletions, insertions, or additions (see page 13), which definition is essentially limitless on the amount of modification to the named structure of SEQ ID NO:2.

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Since the enzyme does not garner a particular structural feature as based on the art, the enzyme name cannot support both a structural and functional limitation for the product of the claimed invention. Furthermore, there is no disclosure of any particular structure to function/activity relationship in the disclosed enzymes. Thus, one of skill in the art would be unable to predict the structure of other members of this genus by virtue of the instant disclosure. The lack of a structure to function/activity relationship in the disclosed enzymes and the lack of representative species for the polynucleotides encoding the enzyme variants as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

*Response to Arguments*

Applicants indicate independent claim 1 has been amended in product-by-process format and incorporates the limitations of claims 4, 16, 18 and 24. In other words, the claims have been amended to recite specific steps for transforming the microorganism to produce the transformant, including the specific sequences, i.e., SEQ ID NOS: 1-6, utilized in the process. Furthermore, the number of modifications is limited to "one to several" and the type of modifications have been defined as "a substitution, a deletion, an insertion, and an addition"; and the functional activity of the enzyme has been included as a positive limitation for the modified sequences as suggested by the Examiner during the interview. In sum, the amended claims are drawn to the specific embodiments, i.e., SEQ ID NOS: 1-6 and the chemical formulae for PF 1022 and the derivative thereof as exemplified in the disclosure. Therefore, written description for the amended claims is satisfied by disclosure (pages 15-17 of the response).

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Applicants' response has been considered, however, the argument is not persuasive regarding the polynucleotides encoding the modified sequence of SEQ ID NO:2, 4 or 6 having the desired enzyme activity because there is no disclosure of any particular structure to function/activity relationship for the disclosed enzymes, and lack of representative species in the specification, one of skill in the art would be unable to identify the structure of a modified enzyme that has desired activity. Although the number of modification and types of modification have been limited somewhat for the modified sequences, there are still unspecified variants encompassed by the claimed invention. Therefore, as indicated above, applicants have failed to sufficiently describe the claimed invention.

13. Previous rejection of claims 1, 5-7, 17 and 19-21 under 35 U.S.C. § 112, first paragraph,, scope of enablement, is maintained, and claims 32, 33 and 35-37 are added, because the specification, while being enabling for transformants of *Mycelia sterilia* containing genes encoding SEQ ID NOs: 2, 4, and 6 that make para-substituted PF1022 wherein the substitution is a -NO<sub>2</sub> or -NH<sub>2</sub> functional group, does not reasonably provide enablement for any transformant to make a peptide or depsipeptide having a benzene ring substituted at para-position with a nitro or amino group using a gene encoding a modified sequence of SEQ ID NO:2 having 4-amino-4-deoxychorismic acid synthase activity, a modified sequence of SEQ ID NO:4 having 4-amino-4-deoxychorismic acid mutase activity, and/or, SEQ ID NO:6 having 4-amino-4-deoxyprephenic acid dehydrogenase activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To make the claims to the full extent of their scope would require undue experimentation.



The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The instant specification teaches the identification of papA, papB, and papC genes in *Streptomyces venezuelae* as found in the vicinity of the known gene pabAB. The pabAB encodes p-aminobenzoic acid synthase; the papA, papB, and papC genes are described as encoding a synthase, a mutase, and a dehydrogenase, respectively (see both Blanc *et al.* and the instant specification) and such activities are distinct from that of pabAB. The papA, papB, and papC genes are described as being analogous to papA, papB, and papC genes from *S. pristinaespiralis*, which microorganism naturally produces pristinamycin - a secondary peptide

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metabolite containing a benzene ring with a para-substituted group that is a nitrogen-containing group (see Blanc *et al.*).

The instant inventors use the papA, papB, and papC genes in a fungus that produces PF1022 (called *Mycelia sterilia* and *Rosellinia sp.* PF1022 in the art) to produce -NO<sub>2</sub> and -NH<sub>2</sub> -para-substituted PF1022 analogs (see Figure 13). These analogs are produced due to the incorporation of the newly produced p-amino-D-phenyllactate that is incorporated into PF1022 in place of D-phenyllactate that is incorporated natively (see Yanai *et al.* 2004, Figure 2). Thus, the teachings of the instant specification enable the production of metabolite analogs wherein the native metabolite incorporates phenyllactate and wherein -NO<sub>2</sub> or -NH<sub>2</sub> analogs are produced using host cells transformed with papA, papB, and papC genes. However, due to the specificity of biosynthetic enzymes, which specificity is well known in the art, other analogs are not enabled and the use of other genes (even the identification of other genes) is not enabled. While one of skill in the art may be able to *find* other papA, papB, and papC genes using hybridization techniques and a knowledge of organisms that may produce/use p-aminophenylpyruvate (the product of the papA-papB-papC pathway), this does not enable one of skill in the art to *make* such genes for use in the claimed transformants because the relevant characteristics of these genes and/or the enzymes they encode so that their functional properties are maintained are unknown. The predictability of the ability of papA, papB, and papC enzymes to incorporate a nitro or amino group in the para position of any peptide or depsipeptide is very, very low.

#### Response to Arguments

Applicants indicate the claims have been amended to the specific transformants of *Mycelia sterilia* containing genes encoding SEQ ID NOS: 2, 4, and 6 and the specifically

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disclosed metabolite, PF1022 and derivative thereof, as defined by their chemical name and formulae. In other words, the amended claims are limited to that which the Examiner indicated is enabled (pages 17-18 of the response).

Applicants' response has been considered, however, the argument is not persuasive because the independent claim 1 is not only directed to transformants of *Mycelia sterilia* containing genes encoding SEQ ID NOS: 2, 4, and 6 and the specifically disclosed metabolite, PF1022 and derivative thereof, but also to the genes encoding modified sequences of SEQ ID NO:2, 4 and 6, and to an unspecified metabolite (i.e., peptide or depsipeptide) having a benzene ring substituted at para-position with a nitro or amino group. Since the correlation of structure and function of these genes is unknown, undue experimentation is required to identify the genes encoding modified sequences of SEQ ID NO:2, 4 and 6 that have desired enzyme activity, thus the full scope of the claims is not enabled as indicated in the section above.

#### ***Claim Rejections - 35 U.S.C. § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Previous rejection of claim 26 under 35 U.S.C. § 102(b) as being anticipated by Blanc *et al.* (Mol. Microbiology 23, 191-202 (1997)) is maintained, and claims 28 and 30 are added. The response to arguments is indicated below.

Claims 26, 28 and 30 encompass a polynucleotide encoding a modified sequence of SEQ ID NO:2 having 4-amino-4-deoxychorismic acid synthase activity, a polynucleotide encoding a

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modified sequence of SEQ ID NO:4 having 4-amino-4-deoxychorismic acid mutase activity, and a polynucleotide encoding a modified sequence of SEQ ID NO:6 having 4-amino-4-deoxyprephenic acid dehydrogenase activity, respectively.

Blanc *et al.* teach the papA gene of *Streptomyces pristinaespiralis* (nucleotides 68-2227) which encodes 4-amino-4-deoxychorismic acid synthase (see abstract and page 196, right column, Fig. 4) that has a modified sequence of SEQ ID NO:2 (see attached sequence alignment; claim 26); the papB gene of *Streptomyces pristinaespiralis* (nucleotides 3413-3802), which encodes 4-amino-4-deoxychorismic acid mutase that has a modified sequence of SEQ ID NO:4 (see attached sequence alignment; claim 28); and the papC gene of *Streptomyces pristinaespiralis* (nucleotides 2486-3376), which encodes 4-amino-4-deoxyprephenic acid dehydrogenase that has a modified sequence of SEQ ID NO:6 (see attached sequence alignment; claim 30).

#### Response to Arguments

Applicants indicate claim 1 has been amended to incorporate the subject matter of claims 10, 12, 14, 16 and 24, which were not included in the rejection, thus, the present amendment overcomes the rejection (pages 18 and 19 of the response).

Applicants' response has been considered, regarding claims 1-5 and 18, the argument is persuasive and the rejection is withdrawn. However, regarding claim 26, the argument is not found persuasive, since Blanc *et al.* teach a papA gene encoding a modified sequence of SEQ ID NO:2 having 4-amino-4-deoxychorismic acid synthase activity, which is the claimed invention.

#### **Conclusion**

15. No claims are allowed

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Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Chih-Min Kam, Ph. D.

CHK

Patent Examiner

CMK

October 10, 2005

  
KATHLEEN M. KERR, PH.D.  
SUPERVISORY PATENT EXAMINER



~~Oct 6 09:19:05 2005~~

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U8-10-089-514-2 (1-686) x SPU60417 (1-4740)

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DB 1409 CGCGCGCTGATCAACCGGCGGAGACCTACAGAGTGAGCTGAGAACATGCTCCGGGTG 1468
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DB 1469 CCGGCGCGGATCAACCGCTTACCGCTTACCGCTGAGCAACCGCTGAGCGCGCC 1528
QY 466 TyGlyValaLeuLeuGluPheProGluLeuSerValLeuSerAlaSerProGluArgPhe 485
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QY 486 LeuThriIleGlyValaAepGlyValaGluSerIleArgProIleGlyThraArgProArg 505
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VERSION M93058.1 GI:153396  
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SOURCE Streptomyces griseus  
ORGANISM Streptomyces griseus  
Bacteria; Actinobacteria; Actinobacteridae; Actinomycetales;  
Streptomyces; Streptomycesaceae; Streptomyces.  
REFERENCE  
AUTHORS Ciriaco, L.M., Martin, J.F. and Gil, J.A.  
TITLE The pab gene of Streptomyces griseus, encoding p-aminobenzoic acid  
biosynthesis, is located between genes possibly involved in candididin  
Gene 126 (1), 135-139 (1993)  
JOURNAL  
ENTRY 93231527

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PUBMED 8472954
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DB 1370 ATGCGCGCGCTTCTGTCGACATCAAGCTCTGTCACCTTCAACCTTCAACCTTCAACCTT 1429  
QY 21 GlyIuAlaThraGlyIleProValValAepAepAepAepAepAepAepAepAepAepAepAep 39





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ACCESSION	AR198353.1				
VERSION	GI:20248202				
KEYWORDS	Unknown.				
SOURCE	Unknown.				
ORGANISM	Unclassified.				
REFERENCE	1 (bases 1 to 2888)				
AUTHORS	Blanc, V., Thibaut, D., Bamae-Jacques, N., Blanche, F., Crozet, J., Barrille, J.-C., Debussche, L., Pamechon, A., Paris, J.-M., and Dutric-Rosset, G.				
TITLE	Strategic program for preparing same by mutasynthesis				
JOURNAL	Patent: US 6352839-A 1 05-MAR-2002;				
FEATURES	Location/Qualifiers				
source	1..2888				

Alignment Scores:	
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V)            --GlyABPrValIInIAIArPGlYrPGIlULeUAlA 59

Zouline, M., Boemare, N., Danchin, A. and Kunst, P.